When does atopic dermatitis warrant systemic therapy?

Recommendations from an expert panel of the International Eczema Council

Simpson, Eric L; Bruin-Weller, Marjolein; Flohr, Carsten; Ardern-Jones, Michael R; Barbarot, Sebastien; Deleuran, Mette; Bieber, Thomas; Vestergaard, Christian; Brown, Sara J; Cork, Michael J; Drucker, Aaron M; Eichenfield, Lawrence F; Foelster-Holst, Regina; Guttman-Yassky, Emma; Nosbaum, Audrey; Reynolds, Nick J; Silverberg, Jonathan I; Schmitt, Jochen; Seyger, Marieke M B; Spuls, Phyllis I; Stalder, Jean-Francois; Su, John C; Takaoka, Roberto; Traidl-Hoffmann, Claudia; Thyssen, Jacob P; van der Schaft, Jorien; Wollenberg, Andreas; Irvine, Alan D; Paller, Amy S

Published in:
Journal of the American Academy of Dermatology

DOI:
10.1016/j.jaad.2017.06.042

Publication date:
2017

Document version
Publisher's PDF, also known as Version of record

When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council

Eric L. Simpson, MD, MCR,[a] Marjolein Bruin-Weller, MD, PhD,[b] Carsten Flohr, MD, PhD, MSc,[c] Michael R. Ardern-Jones, DPhil(PhD), FRCP(MD),[d] Sebastien Barbarot, MD, PhD,[e] Mette Deleuran, MD, DMSc,[f] Thomas Bieber, MD, PhD, MDRA,[g,h] Christian Vestergaard, MD, PhD, DMSc,[i] Sara J. Brown, MD, FRCPE,[j,k] Michael J. Cork, PhD, FRCP,[l] Aaron M. Drucker, MD, FRCPC,[m] Lawrence F. Eichenfield, MD,[n,o,p] Regina Foelster-Holst, MD,[q] Emma Guttman-Yassky, MD, PhD,[r] Audrey Nosbaum, MD, PhD,[s] Nick J. Reynolds, MD, FRCP,[t,u] Jonathan I. Silverberg, MD, PhD, MPH,[v,w,x] Jochen Schmitt, MD, MPH,[y] Marieke M. B. Seyger, MD, PhD,[z] Phyllis I. Spuls, MD, PhD,[aa] Jean-Francois Stalder, MD,[e] John C. Su, MD, MEpi, MA, MSt,[bb,cc] Roberto Takaoka, MD,[dd] Claudia Traidl-Hoffmann, MD,[ee,ff] Jacob P. Thyssen, MD, PhD, DmSci,[gg] Jorien van der Schaft, MD, PhD,[hh] Andreas Wollenberg, MD, DrMed, DrHC,[ii] Alan D. Irvine, MD, DSc,[jj] and Amy S. Paller, MSc, MD[v,kk,ll]

Portland, Oregon; Utrecht, Nijmegen, and Amsterdam, The Netherlands; London, Southampton, Dundee, Sheffield, Newcastle upon Tyne, and Dublin, United Kingdom; Nantes, France; Aarhus and Hellerup, Denmark; Davos, Switzerland; Providence, Rhode Island; San Diego, California; Bonn, Kiel, Dresden, and Munich, Germany; New York and Rochester, New York; Lyon, France; Chicago, Illinois; Melbourne, Australia; and São Paulo, Brazil

Background: Although most patients with atopic dermatitis (AD) are effectively managed with topical medication, a significant minority require systemic therapy. Guidelines for decision making about advancement to systemic therapy are lacking.

Objective: To guide those considering use of systemic therapy in AD and provide a framework for evaluation before making this therapeutic decision with the patient.

From the Department of Dermatology, Oregon Health and Science University, Portland[a]; National Expertise Center for Atopic Dermatitis, Department of Dermatology and Allergology, University Medical Center Utrecht[b]; Unit for Population-Based Dermatology Research, St John's Institute of Dermatology, Guy's and St Thomas' National Health Service Foundation Trust and King's College London[c]; Clinical Experimental Sciences, Faculty of Medicine, University of Southampton[d]; Department of Dermatology, Nantes University Hospital[e]; Department of Dermatology, Aarhus University Hospital[f]; Department of Dermatology and Allergy, University of Bonn[g]; Christine Kühne-Center for Allergy Research and Education, Davos[h]; Department of Dermatology Aarhus University Hospital[i]; Skin Research Group, School of Medicine, University of Dundee[j]; Department of Dermatology, Ninewells Hospital and Medical School, Dundee[k]; Sheffield Dermatology Research Department of Infection, Immunity and Cardiovascular Disease, The University of Sheffield[l]; Department of Dermatology, Alpert Medical School of Brown University, Providence[m]; Department of Dermatology[n] and Department of Pediatrics, University of California, San Diego[o]; Rady Children's Hospital, San Diego[p]; Dermatology, Venereology and Allergology, University of Schleswig-Holstein, Kiel[q]; Icahn School of Medicine at Mount Sinai Medical Center, New York[r]; Department of Allergy and Clinical Immunology, University Hospital Lyon Sud, Hospices Civiles de Lyon[s]; Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne[t]; Newcastle Dermatology, Royal Victoria Infirmary, Newcastle upon Tyne[u]; Department of Dermatology,[v] Department of Preventive Medicine,[w] and Department of Medical Social Sciences,[x] and Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago[kk]; Center for Evidence-Based Healthcare, Technische Universität Dresden[y]; Department of Dermatology, Radboud University Nijmegen Medical Centre[z]; Department of Dermatology, Academic Medical Centre, Amsterdam[aa]; Department of Dermatology[bb] and Department of Paediatrics, Monash University, Eastern Health and Murdoch Childrens Research Institute, University of Melbourne[cc]; Department of Dermatology, University of São Paulo Medical School[dd]; Institute of Environmental Medicine, UNIKA-T, Technical University of Munich and Helmholtz Zentrum München—German Research Center for Environmental Health (GmbH), Munich[ee]; CK CARE, Christine-Kühne-Center for Allergy Research and Education, Davos[ff]; Department of Dermatology and Allergy, Herlev-Gentofte Hospital, University of Copenhagen, Hellerup[gg]; Department of Dermatology and Allergology, University Medical Centre Utrech[hh]; Department of Dermatology and Allergy, Ludwig-Maximilian-University Munich[ii]; Trinity College Dublin, National Children's Research Centre, Paediatric Dermatology Our Lady's Children's Hospital, Dublin[jj]; and Ann and Robert H. Lurie Children's Hospital of Chicago.[ll]

Methods: A subgroup of the International Eczema Council determined aspects to consider before prescribing systemic therapy. Topics were assigned to expert reviewers who performed a topic-specific literature review, referred to guidelines when available, and provided interpretation and expert opinion.

Results: We recommend a systematic and holistic approach to assess patients with severe signs and symptoms of AD and impact on quality of life before systemic therapy. Steps taken before commencing systemic therapy include considering alternate or concomitant diagnoses, avoiding trigger factors, optimizing topical therapy, ensuring adequate patient/caregiver education, treating coexistent infection, assessing the impact on quality of life, and considering phototherapy.

Limitations: Our work is a consensus statement, not a systematic review.

Conclusion: The decision to start systemic medication should include assessment of severity and quality of life while considering the individual's general health status, psychologic needs, and personal attitudes toward systemic therapies. (J Am Acad Dermatol 2017;77:623-33.)

Key words: atopic dermatitis; azathioprine; biologic; consensus statement; cyclosporine; eczema; methotrexate; quality of life; systemic therapy.

Drs Irvine and Paller contributed equally to this article.

Corporate sponsorship was provided to the International Eczema Council by Abbvie, Amgen, Celgene, Chugai, Galderma, GlaxoSmithKline/Stiefel, the Leo Foundation, Leo Pharma, Lilly, MedImmune/Astrazeneca, Pfizer, Sanofi, Genzyme and Regeneron Pharmaceuticals, and Valeant. The sponsors had no influence on the content and viewpoints in this article. The cost of publication was covered by the International Eczema Council.

Disclosure: Dr Simpson is an investigator for GlaxoSmithKline, Novartis, Regeneron, Vanda, and Tioga and a consultant with honorarium for Celgene, Galderma, Dermira, Genentech, GlaxoSmithKline, Pfizer, Regeneron, and Sanofi. Dr Bruin-Weller is an investigator for Roche and an investigator and consultant for Abbvie and Regeneron/Sanofi, with all fees paid to her institution. Dr Flohr is a consultant with honorarium for Roche/Genentech and Sanofi/Regeneron. Dr Barbarot is a consultant with honorarium for Pierre Fabre Laboratory and Sanofi-Genzyme, a speaker/educator with honorarium for Bioderma, and an investigator with Pierre Fabre Laboratory. Dr Deleuran is an investigator for AbbVie and Sanofi Genzyme and a consultant with honorarium for CKCare Foundation, La Roche Posay, Leo Pharma, Meda Pharma, Pierre Fabre, Regeneron, and Sanofi Genzyme. Dr Bieber is an investigator or consultant or lecturer for Sanofi, Regeneron, Novartis, Roche, Astellas, Galderma, Pfizer/Anacor, GlaxoSmithKline, Lilly, and L'Oréal. Dr Cork is a consultant with honorarium and investigator for Regeneron and Sanofi. Dr Drucker is a consultant with honorarium for Astellas Canada, Prime Inc, Sanofi, and Spire Learning and an investigator for Sanofi and Regeneron. Dr Eichenfield is a consultant with honorarium for Anacor/Pfizer, Galderma, Genentech, Lilly, Regeneron/Sanofi, and Valeant and an investigator for Regeneron/Sanofi. Dr Foelster-Holst is an investigator (with fees paid to her institution) for Astellas, Novartis Pharma, Phamanet, Pierre Fabre, and Regeneron and a consultant with honoraria for ALK/Abbott, Ardeypharm, Astellas, Johnson and Johnson, La Roche Posay, and Neubourg Skin care GMBH and Co. Dr Guttman is a consultant with honorarium for AbbVie, Allergan, Amgen, Anacor, Bristol-Myers Squibb, Celgene, Celsus Therapeutics, Dermira, Drais, Eli Lilly, Escalier, Galderma, Genentech, Glenmark, LEO Pharma, Mitsubushi Tanabe, Novartis, Pfizer, Regeneron, Sanofi, Stiefel/GlaxoSmithKline, and Vitae and principal investigator for Bristol-Myers Squibb, Celgene, Dermira, Janssen Biotech, LEO Pharma, Merck, Novartis, and Regeneron. Dr Nosbaum is a consultant with honorarium for Sanofi. Dr Reynolds is an investigator for BBSRC Case with AstraZeneca, Stiefel/GlaxoSmithKline, Bristol Myers Squib, Genentech, Innovate UK with Stiefel/GlaxoSmithKline, and Wellcome Trust/GlaxoSmithKline and a consultant with honorarium for Genentech. Dr Schmitt is an investigator for ALK, Merck Sharp and Dohme, Novartis, Pfizer, and Sanofi and a consultant with honorarium for Novartis and Roche. Dr Spuls is a consultant with honorarium for AbbVie, Anacor, Leo Pharma, and Novartis and an investigator for Leopharma and Schering Plough; she reports also having been involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of psoriasis and atopic dermatitis. Dr Thyssen is a consultant with honorarium for Leo Pharma, Roche, and Sanofi-Genzyme. Dr Wollenberg is a consultant with honorium for Almiral, Anacor, Astellas, Bioderma, Celgene, Chugai (travel grant), Galderma, Hans Karrer, Leo Pharma, L'Oreal, MEDA, MedImmune, Merck Sharp and Dohme, Novartis, Pierre Fabre, Pfizer, Regeneron, and Sanofi-Adventis and he received research funding from Beiersdorf and Leo Pharma. Dr Irvine is a consultant with honorarium for AbbVie, Anacor, Chugai Pharma, Genentech, and Sanofi Regeneron. Dr Paller is a consultant with honorarium Anacor, Eli Lilly, Galderma, GlaxoSmithKline/Stiefel, Pierre Fabre, Puricore, Regeneron/Sanofi, Roivant, and Valeant and an investigator for Astellas and Pfizer. Drs Ardern-Jones, Vestergaard, Brown, Silverberg, Seyger, Stalder, Su, Takaoka, Traidl-Hoffmann, and Van der Schaft have no conflicts of interest to declare.

Accepted for publication June 19, 2017

Reprints not available from the authors.

Correspondence to: Eric L. Simpson, MD, MCR, Department of Dermatology, Oregon Health and Science University, Portland, OR. E-mail: simpsone@ohsu.edu. Alan D. Irvine, MD, DSc, Trinity College Dublin, National Children's Research Centre, Paediatric Dermatology, Our Lady's Children's Hospital, Dublin, United Kingdom. E-mail: irvinea@tcd.ie. Amy S. Paller, MSc, MD, Department of Dermatology, Northwestern University Feinberg School of Medicine, 676 N St Clair, Suite 1600, Chicago, IL 60611. E-mail: apaller@northwestern.edu.

Published online August 10, 2017.

0190-9622

http://dx.doi.org/10.1016/j.jaad.2017.06.042

Most patients with atopic dermatitis (AD) have mild-to-moderate disease[1] that responds adequately to optimized emollient use, avoidance of irritants and disease triggers, and standard topical anti-inflammatory therapies. However, many patients with AD may not have adequate disease control with these regimens of care or with phototherapy. For pediatric and adult patients with moderate-to-severe AD that does not respond to topical therapy and for which phototherapy is not a viable option, systemic therapy is needed to control skin inflammation, reduce symptoms, prevent flares, and improve quality of life (QoL). The decision to initiate a systemic medication for AD can be difficult, given the known risks of traditional immunosuppressants. In a study from Germany, 10% of patients with AD received systemic therapy with oral corticosteroids,[2] although the proportion of children with AD requiring systemic therapy is likely lower.[3,4]

CAPSULE SUMMARY

- Physicians should optimize topical therapy before considering systemic medications for atopic dermatitis.
- Patients who fail to respond should be evaluated for exacerbating factors such as cutaneous infection and for alternative diagnoses such as allergic contact dermatitis.
- The decision to start systemic therapy depends on disease severity, impact on quality of life, and risks and benefits of systemic therapies for the individual patient.

Recent guidelines and systematic reviews from national societies provide evidence-based summaries of the safety and efficacy of systemic agents used for AD treatment,[5-9] and others discuss how systemic treatments can be used effectively.[10] Nevertheless, the question of *when* a patient is a candidate for systemic therapy has received little attention.[11]

Clinicians, patients, and caregivers consider many factors when deciding whether a systemic agent should be used. Most reviews state that failure to respond to adequate topical therapy, need for prolonged use of high-potency topical steroids, or repeated flares makes a patient eligible, but there are no universally accepted definitions of recalcitrance. Given the lack of clarity in decision making and in an effort to prevent overtreatment or undertreatment, a group of experts on AD management, all councilors or associates of the International Eczema Council (IEC), conferred to provide consensus guidance for clinicians in recognizing when a child or adult is considered a candidate for systemic therapy.

METHODS

Authors participated in a face-to-face meeting to delineate broad topic areas for consideration before prescribing systemic therapy. Topic areas (the section subheadings of this consensus statement) were assigned to expert reviewers from 9 countries, each of whom performed a literature review, referred to guidelines when available, and provided interpretation and expert opinion on that topic area.

RESULTS

This expert review group recommends a systematic approach to assess patients with severe signs and/or symptoms of AD and/or impact on quality of life before systemic therapy. We reviewed the strengths and weaknesses of methods to measure disease severity and discussed issues to address before determining that nonsystemic treatment had failed. Finally, we summarized the key steps to follow before choosing to start a systemic agent (Fig 1). Consensus across these areas is detailed in the following sections.

Severity-based scoring systems alone cannot determine the need for systemic therapy: a holistic assessment is needed

One approach for identifying a candidate for systemic therapy is to utilize a disease severity score. More than 20 AD scoring systems quantify disease severity.[12,13] The 2 most extensively validated are the Scoring of Atopic Dermatitis (SCORAD), which incorporates the intensity of disease signs and extent along with the patient-reported sleep loss and itch, and the Eczema Area and Severity Index.[14] Scoring systems are used primarily in clinical trials and are too time-consuming for routine clinical practice. Moreover, these tools assess only part of the complex thinking that underlies treatment selection.

Assessment of the impact of AD on the patient, however, needs to include consideration of *both* severity and quality of life. Even if the extent of disease is small (eg, just the face, hands, or genital area), the impact on the individual patient may still be severe, negatively affecting a patient's emotional state, social functioning, activities of daily living, or any combination of these. Furthermore, extent of AD is hard to quantify because lesions are diffuse and less circumscribed than in psoriasis, for example. Using a SCORAD higher than 25 to define moderate-to-severe disease is favored by many European

Abbreviations used:

AD:	atopic dermatitis
IEC:	International Eczema Council
NB-UVB:	narrowband ultraviolet B
QoL:	quality of life
SCORAD:	SCORing Atopic Dermatitis Score
TCI:	topical calcineurin inhibitors
TCS:	topical corticosteroid

dermatologists,[15,16] but our expert panel identified several drawbacks to the use of a single scoring system in identifying candidates for systemic treatment.

A single, static (1 point in time) measurement of severity may overestimate or underestimate the true AD severity experienced by the patient, given the characteristic exacerbations and remissions of AD.[17] Serial measurements can provide information about baseline severity, flares, and therapeutic response. It is important to gauge the severity and frequency of disease flares by using a variety of methods, as flares are a major determinant of quality of life and disillusionment with current therapy.[18] Self-assessment scores such as the Patient-Oriented Eczema Measure and Patient-Oriented SCORAD enable patient-derived assessment of the course of the disease between consultations.[19-21] Documentation of severe, extensive disease and/or QoL impairment at several time points with adequate topical therapy enables a holistic rationale for moving to systemic therapy.

Assess disease impact on QoL

AD can severely affect social lives and emotional well-being, as well as academic and occupational endeavors.[22] Validated QoL measures can be useful, but their use in the clinic may not be practical. For example, Heinl et al identified the best-validated instrument for measuring QoL with pediatric AD to be the Childhood Atopic Dermatitis Impact Scale, which contains more than 30 items.[23] In some practice settings, shorter, yet validated QOL scales, such as the Dermatology Life Quality Index or Skindex-16, may be useful to help document the impact of the disease, which may not be readily apparent through routine questioning. Chernyshov et al recently reviewed the pros and cons of the various instruments available for QOL measurement in AD.[24] Alternatively, clinicians may assess and document QoL by using simple, open-ended questions, such as How is your atopic dermatitis affecting you? or How does your atopic dermatitis affect your life at home or at school/work? The frequency and intensity of symptoms, such as itch, pain, and sleep disruption can be assessed by using formal tools such as the Patient-Oriented Eczema Measure, visual analogue scales, or numeric rating scales.[25] Treatment burden includes the time spent on treatment and the costs of medications, physician visits related to AD flares, and medication monitoring. If the impact on QoL from symptoms and/or treatment burden is significant in the eyes of the patient despite efforts to establish an appropriate and feasible plan of topical care (further discussed later), systemic therapy should be considered and may be more acceptable to patients and providers alike.

Alternative or concomitant diagnoses should be considered before advancing to systemic therapy

The diagnosis of AD is usually made clinically. However, a correct diagnosis can sometimes be challenging, particularly if clinical features are atypical (Table I). Careful history taking, examination, and (sometimes) accompanying biopsy, laboratory assessments such as potassium hydroxide, scabies microscopic examinations, or patch testing[26] should be undertaken.

Ensure that adequate education has been delivered to improve adherence to topical therapy

It is important to ascertain whether failure of topical treatment is due to the severity of the disease (lack of efficacy of topical therapy) or lack of adherence to the treatment when making the decision to begin systemic therapy. Adherence to optimal topical management is challenging and can be exhausting for some patients and caregivers. Most prevalent is the fear of patients, caregivers, and health professionals about use of topical anti-inflammatory medications.[27] However, the smell and stains from tar preparations, the "feel" of a topical ointment (vs an oil or cream), and the messiness of certain topicals under clothes are patient concerns that can be discussed and accommodated to improve adherence. In addition to steroid phobia,[28] there is fear of topical calcineurin inhibitors (TCIs) related to the black box warning mandated by the US Food and Drug Administration in 2005. Although the black box warning was initiated because of the theoretical risk of malignancy, no signal for cancer risk has emerged; nevertheless, the black box remains and requires US pharmacists to warn patients.

If failure of therapy is due to lack of adherence and/or topical corticosteroid (TCS) phobia, the first-line intervention of choice is patient education.[29-32] If adherence to topical therapy cannot be optimized

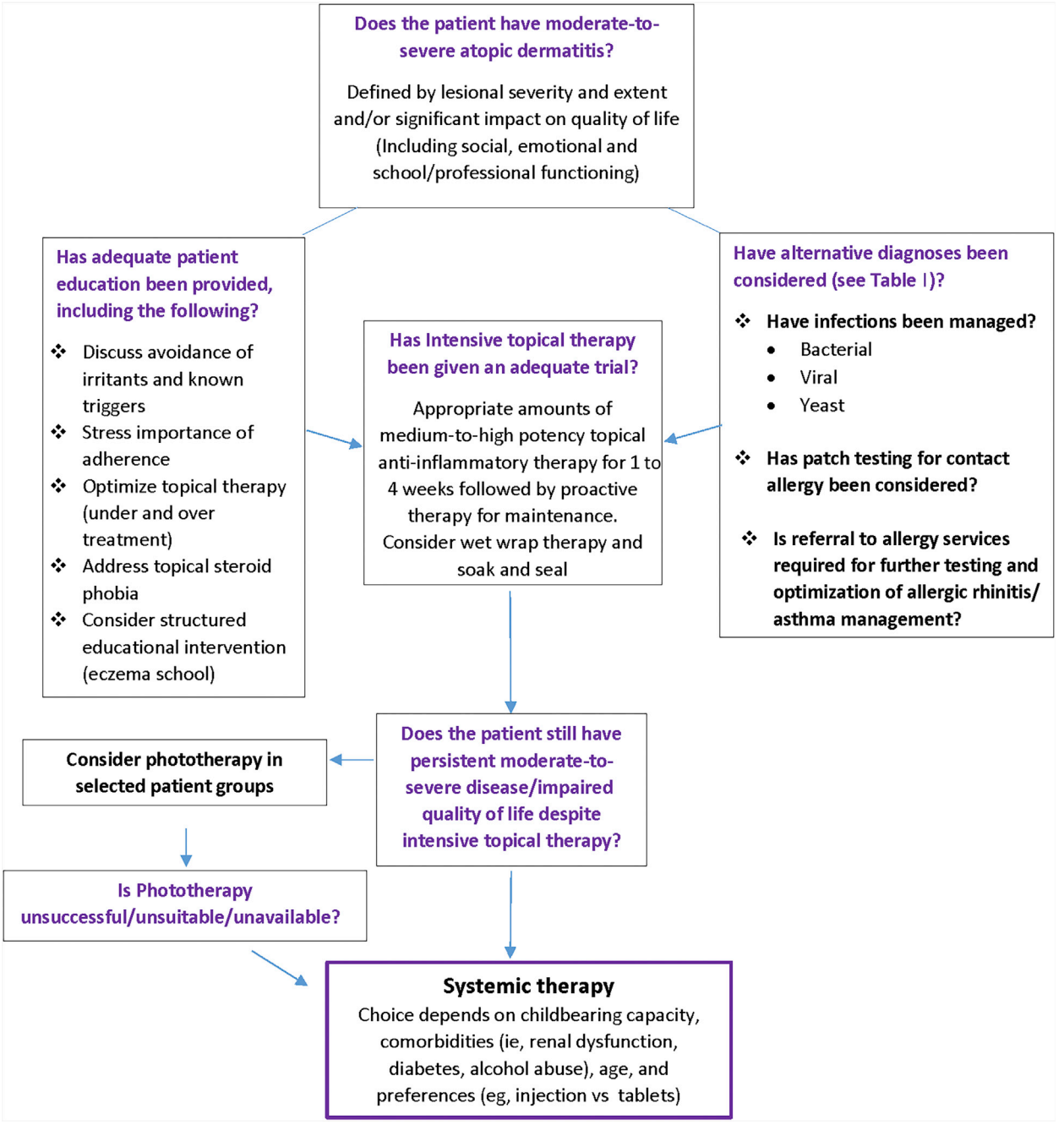

Fig 1. Algorithm to decide when systemic immunomodulatory therapy is warranted in patients with atopic dermatitis.

despite proper education, the decision to start systemic therapy rests on the clinician's understanding of the reasons for continued nonadherence and whether those reasons can justify the risk and expense of systemic therapy for a particular patient. The need for overly complex topical regimens that are not feasible for a particular patient may justify moving to systemic therapy.

There are no evidence-based recommendations for environmental trigger avoidance measures in patients with AD. However, several factors potentially provoke flares, most commonly, irritants such as detergents, sweat, saliva, aeroallergens, contact allergens, and psychologic stress.[33]

Patients need a trial of intensive topical therapy

We advocate comprehensive patient education and a period of intensive topical therapy (if needed in a daycare setting), followed by reassessment of the

Table I. Differential diagnoses to consider in pediatric and adult patients with severe atopic dermatitis

Condition	Clinical features	Diagnostic work-up
Children and adults		
Contact dermatitis (irritant or allergic)	Atypical or localized distribution	Patch testing for allergic contact
Severe, suberythrodermic psoriasis	Less pruritus and lack of eczematous change such as oozing/crusting	Biopsy
Severe seborrheic dermatitis	Lack of pruritus with greasy scale in scalp and folds in infants	Clinical diagnosis
Scabies infestation	Inguinal, axillary, and genital papules. Palmoplantar vesicles and burrows in infants.	Mineral oil scraping
Widespread tinea corporis	Annular papulosquamous lesions without eczematous change	Skin scraping for microscopy and culture
Children		
Zinc deficiency	Erosive plaques on face and groin with fussiness	Zinc levels and genetic testing
Netherton syndrome/other ichthyoses	Erythroderma, hair abnormalities, and failure to thrive	Genetic testing
Immune deficiencies (eg, severe combined immunodeficiency, agammaglobulinemia, Wiskott-Aldrich syndrome, hyperIgE syndrome)	Sinopulmonary infections and failure to thrive	Genetic and immunologic testing, as well as total IgE (hyperIgE syndrome)
Adults		
Cutaneous T-cell lymphoma	Lack of classic eczematous skin changes such as oozing and crusting	Skin biopsy and T-cell rearrangement studies

IgE, Immunoglobulin E.

disease impact on severity and quality of life.[15] Authors agreed that the general approach should be an intensive clearance period with a TCS followed by a safe and individualized regimen of intermittent TCSs, TCIs, or emollients to prevent flares. The strength of prescribed TCSs should be appropriate for patient age and the body locations being treated. Exact treatment protocols varied among the authors, but there was general consensus that the use of more potent TCSs (medium- to high-potency, class I to III in the United States, and class III to IV in Europe) once or twice daily for 1 to 4 weeks provides a useful way to gain control of severe disease, followed by a taper in application frequency. Patient age should be taken into consideration, with use of the strongest steroid classes restricted to adolescents and adults. Wet-wrap therapy and use of therapy after soaking in a bath (particularly in cases in children) may also be useful adjunctive measures to the application of TCSs or TCIs to quickly reduce disease severity but will increase the potency of the treatment.[34]

Should a patient improve during this induction period, it may be possible to maintain disease control by utilizing a medium-strength TCS or TCI applied 2 to 3 times weekly to *normal-appearing skin* at a site of frequent flares (proactive therapy).[35-38] This approach has been shown to significantly reduce relapses, ultimately requiring less total TCS/TCI with negligible side effects.[39] Patients who flare frequently, despite TCS induction followed by a proactive approach, are candidates for systemic therapy. Overuse of topical therapy (potency, frequency, and duration) despite controlled disease represents an indication for systemic therapy. Finally, the need for repeated courses of oral or intramuscular steroids, a management strategy discouraged by AD treatment guidelines, would be another indication for initiating more appropriate systemic therapy.

Infection should be sought and treated as appropriate

Bacterial or viral infections should be identified and treated before considering systemic therapy. Many individuals affected by AD have skin and nasal colonization with *Staphylococcus aureus,*[40] increasing the risk of cutaneous infection.[41] Furthermore, AD flares are accompanied by a shift in the microbiome, with an increased percentage of *S aureus* and reduced bacterial diversity.[42] Certain viral infections have also been associated with AD

Table II. Most common on-label and off-label systemic therapies in AD

Drug (in alphabetical order)	Approved for AD?	Estimated efficacy (% reduction in composite severity scores)	Dose range	Common or serious side effects	Monitoring required*
Azathioprine	No	26%-39%[5]	Adult: 1-3 mg/kg/day; Pediatric: 1-4 mg/kg/day	Hematologic abnormalities, skin and other malignancies, hepatosplenic lymphoma, and CNS infections such as PML	CBC, CMP, thiopurine methyltransferase
Cyclosporine	No in United States, yes in Europe	53%-95%[5]	Adult and pediatric: 2.5-5 mg/kg	Renal insufficiency, hypertension, and drug interactions	CBC, CMP, magnesium, uric acid, lipids, and blood pressure
Dupilumab	Yes	73%[62]	Adult: 600 mg loading followed by 300 mg/wk	Injection site reactions and conjunctivitis	None
Methotrexate	No	42%[5]	Adult: 7.5-25 mg weekly Pediatrics: 0.2-0.7 mg/kg weekly	Hepatoxicity, hematologic abnormalities, teratogen, gastrointestinal intolerance, nausea, and fatigue	CBC, CMP
Mycophenolate	No	Unknown	1.0-1.5 g orally twice daily Pediatric: 30-50 mg/kg daily	Gastrointestinal, teratogen	CBC, CMP

AD, Atopic dermatitis; *CBC*, complete blood count with differential and platelets; *CMP*, complete metabolic panel with basic chemistries and liver function tests; *CNS*, central nervous system; *PML*, progressive multifocal leukoencephalopathy.
*See published review by Sidbury et al[7] for more complete and detailed information regarding dosing and drug monitoring.

exacerbation (eczema herpeticum, eczema coxsackium, and molluscum).[43]

Systemic antibiotics are usually required for treatment of cutaneous bacterial infection, especially before initiation of systemic therapy,[11] as persistent infection may impair treatment responses.[44] Systemic antibiotics should be avoided in the absence of signs of infection (ie, these should not be used as a systemic treatment for AD and do not effectively reduce *S aureus* colonization).[45] Antiseptic baths, most commonly with 0.005% sodium hypochlorite (dilute bleach), reduce disease severity[46] and could be considered before systemic therapy, although this approach is not universally adopted and may have a greater ameliorative effect on the barrier and inflammation than on *S aureus* colonization. Topical or even systemic antifungal treatment could be considered for head and neck dermatitis, which is postulated to be driven by secondary yeast colonization, although the results of clinical trials have been conflicting.[47]

Possible allergic triggers should be considered and managed as appropriate

Patients with AD have a higher rate of allergic sensitization, including both type I reactions to aeroallergens (eg, animal dander and grass pollens) and type IV delayed allergic responses to contact allergens. Fragrances, preservatives (particularly propylene glycol and methylchlorothiazolinone) and emulsifiers in emollients and topical steroid creams are a frequent source of contact allergens for patients with AD.[25,48-51] If the patient's history and physical examination results suggest allergic triggers that exacerbate disease, further investigation to identify these triggers is appropriate (eg, referral to allergy services for skin prick testing or patch testing).

Phototherapy should be considered before the use of other systemic therapy if accessible and practical

Phototherapy is recommended as second-line or adjuvant therapy in selected patients for moderate-to-severe AD, especially in adults and older children.[7,52] Systematic reviews have identified the greatest efficacy for narrowband ultraviolet B (NB-UVB) (311-313 nm) and ultraviolet A-1 (340-400 nm).[53,54] Psoralen with ultraviolet A radiation is associated with a greater risk of cutaneous malignancy and should be considered only in adults for whom NB-UVB has shown inadequate efficacy.[55] Phototherapy is also efficacious in the pediatric population,[7,56] but the long-term risk of skin cancer, especially in fair-skinned individuals, is not fully understood, suggesting the need for caution in this population, especially in patients who might receive systemic immunosuppressive medication later in life.

Optimal benefit requires a prolonged course (~24 phototherapy treatments) to induce sustained remission, and adherence to phototherapy can be particularly challenging. Phototherapy is often poorly tolerated in highly inflamed AD and may be better tolerated after acute disease control with intensive topical or wet-wrap therapy.

Typically, 2 or 3 treatments per week of NB-UVB are used for 6 to 12 weeks[57] or longer.[7] If no response is seen within 8 to 12 weeks, or if AD recurrently flares during phototherapy, we recommend discontinuation. If AD improves with phototherapy but relapses rapidly, the safety risks of frequent retreatment or use of maintenance phototherapy must be weighed against those of systemic therapy. For many patients, the inconvenience of office-based phototherapy is untenable and home phototherapy may be a useful option; 1 study of patients with psoriasis showed results of home phototherapy similar to those of in-office use.[58]

Phototherapy should be discontinued if cyclosporine or other systemic treatments (eg, azathioprine or mycophenolate mofetil) are initiated to avoid the synergistic risk of inducing skin malignancy. Combining methotrexate with phototherapy is thought to be associated with lower risk than other immunosuppressants and has been used for psoriasis treatment.[59]

Factors to consider when choosing a systemic agent

Each patient's situation is unique, and several factors influence the discussion between patient/caregiver and physician that leads to therapeutic decision making.[60] These include existent comorbidities and results of baseline investigations; patient age; anticipation of pregnancy and family planning issues for both male and female patients; and the patient's previous clinical experience, including with systemic agents.[61] Sharing information about treatment efficacy and potential side effects with the patient and family is also important. The most commonly used systemic medications for AD are summarized in Table II. A shared decision-making process should then be undertaken, weighing these factors previously discussed herein with the risks and benefits of the individual agents. The actual choice of any 1 systemic agent is beyond the scope of this article.

A future consideration: will the availability of targeted immunomodulation with fewer safety risks lower the threshold for utilization of systemic agents?

Several emerging therapies are showing evidence of efficacy and short-term safety that are potentially

superior to those of traditional immunosuppressive therapy.[62] Prospective registries will be useful to assess long-term safety and efficacy profiles, ideally allowing comparisons between conventional systemic immunosuppressants and novel emerging agents. The Treatment of Atopic Eczema Registry Taskforce has just reached consensus on a core data set for prospective registries for phototherapy and systemic therapies to facilitate comparison and pooling of data, should more than 1 registry be established.[63]

If proven both efficacious and safer than conventional immunosuppressive therapies (both short- and long-term therapy), systemic biologic and small-molecule therapies could lower the bar toward use for more moderate disease, not only to improve disease response and quality of life, but also to potentially prevent disease progression and future comorbidities. The long-term safety and accessibility of these newer interventions will enter into the decision-making equation for patients in the future.

CONCLUSION

This article provides a framework of thinking to inform patients and physicians confronted with the possibility of commencing systemic therapies for severe AD in adult or pediatric practice. We purposely offered no definitive Boolean yes/no guidelines, but have instead offered guidance on the complex considerations in making this decision (Fig 1). The decision to start a systemic agent should ideally include assessments of severity and quality of life, while also allowing consideration of individual factors. Some of these additional individual factors are patient preferences, impact on personal life, prior topical therapy, financial implications, and comorbidities. The ultimate decision to commence systemic therapy will depend on the joint exploration of these many factors by the patient/caregiver and providers, taking into account the patient's psychologic needs, disease severity, and personal attitudes to systemic therapies.

We acknowledge the following IEC associates and councilors for their important contributions to the concepts in this article: Lisa Beck, Rochester, New York; Robert Bissonnette, Montreal, Canada; Anna De Benedetto, Gainesville, Florida; Kyu Han, Seoul, South Korea; Emmilia Hodak, Tel Aviv, Israel; Kenji Kabashima, Kyoto, Japan; Kwan Hoon Lee, Yonsei, Korea; Thomas Luger, Muenster, Germany; Cheng-Che E. Lan, Kaohsiung, Taiwan; Johannes Ring, Munich, Germany; Seong Jun Seo, Seoul, South Korea; Georg Stingl, Vienna, Austria; and Alain Taieb, Bordeaux, France. Sara J. Brown holds a Wellcome Trust Senior Research Fellowship in Clinical Science (106865/Z/15/Z). We appreciate the assistance of Margaret Jung, IEC executive director, in organizing councilor responses.

REFERENCES

1. Silverberg JI, Simpson EL. Associations of childhood eczema severity: a US population-based study. *Dermatitis*. 2014;25:107-114.
2. Schmitt J, Schmitt NM, Kirch W, Meurer M. Outpatient care and medical treatment of children and adults with atopic eczema. *J Dtsch Dermatol Ges*. 2009;7:345-351.
3. McAleer MA, Flohr C, Irvine AD. Management of difficult and severe eczema in childhood. *BMJ*. 2012;345:e4770.
4. Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. *Br J Dermatol*. 1998;139:73-76.
5. Roekevisch E, Spuls PI, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. *J Allergy Clin Immunol*. 2014;133:429-438.
6. Nankervis H, Thomas KS, Delamere FM, Barbarot S, Rogers NK, Williams HC. *Programme Grants for Applied Research. Scoping systematic review of treatments for eczema*. Southampton, UK: NIHR Journals Library; 2016.
7. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014;71:327-349.
8. Saeki H, Nakahara T, Tanaka A, et al. Clinical practice guidelines for the management of atopic dermatitis 2016. *J Dermatol*. 2016;43:1117-1145.
9. Galli E, Neri I, Ricci G, et al. Consensus Conference on Clinical Management of pediatric Atopic Dermatitis. *Ital J Pediatr*. 2016;42:26.
10. Flohr C, Irvine AD. Systemic therapies for severe atopic dermatitis in children and adults. *J Allergy Clin Immunol*. 2013;132:774-774.e6.
11. Arkwright PD, Motala C, Subramanian H, et al. Management of difficult-to-treat atopic dermatitis. *J Allergy Clin Immunol Pract*. 2013;1:142-151.
12. Schmitt J, Langan S, Deckert S, et al. Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation. *J Allergy Clin Immunol*. 2013;132:1337-1347.
13. Ganemo A, Svensson A, Svedman C, Gronberg BM, Johansson AC, Wahlgren CF. Usefulness of Rajka and Langeland eczema severity score in clinical practice. *Acta Derm Venereol*. 2016;96:521-524.
14. Schmitt J, Langan S, Williams HC, Network ED-E. What are the best outcome measurements for atopic eczema? A systematic review. *J Allergy Clin Immunol*. 2007;120:1389-1398.
15. Wollenberg A, Oranje A, Deleuran M, et al. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol*. 2016;30:729-747.
16. Oranje AP, Glazenburg EJ, Wolkerstorfer A, de Waard-van der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. *Br J Dermatol*. 2007;157:645-648.
17. Haeck IM, ten Berge O, van Velsen SG, de Bruin-Weller MS, Bruijnzeel-Koomen CA, Knol MJ. Moderate correlation between quality of life and disease activity in adult patients with atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2012;26:236-241.
18. Zuberbier T, Orlow SJ, Paller AS, et al. Patient perspectives on the management of atopic dermatitis. *J Allergy Clin Immunol*. 2006;118:226-232.
19. Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. *Br J Dermatol*. 2013;169:1326-1332.

20. Coutanceau C, Stalder JF. Analysis of correlations between patient-oriented SCORAD (PO-SCORAD) and other assessment scores of atopic dermatitis severity and quality of life. *Dermatology*. 2014;229:248-255.
21. Stalder JF, Barbarot S, Wollenberg A, et al. Patient-oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe. *Allergy*. 2011;66:1114-1121.
22. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK, Qureshi AA. The burden of atopic dermatitis: summary of a report for the National Eczema Association. *J Invest Dermatol*. 2017;137:26-30.
23. Heinl D, Prinsen CA, Sach T, et al. Measurement properties of quality-of-life measurement instruments for infants, children and adolescents with eczema: a systematic review. *Br J Dermatol*. 2017;176:878-889.
24. Chernyshov PV, Tomas-Aragones L, Manolache L, et al. Quality of life measurement in atopic dermatitis. Position paper of the European Academy of Dermatology and Venereology (EADV) Task Force on Quality of Life. *J Eur Acad Dermatol Venereol*. 2017;31(4):576-593.
25. von Kobyletzki LB, Thomas KS, Schmitt J, et al. What factors are important to patients when assessing treatment response: an international cross-sectional survey. *Acta Derm Venereol*. 2017;97:86-90.
26. Chen JK, Jacob SE, Nedorost ST, et al. A pragmatic approach to patch testing atopic dermatitis patients: clinical recommendations based on expert consensus opinion. *Dermatitis*. 2016;27:186-192.
27. Farrugia LL, Lee A, Fischer G, Blaszczynski A, Carter SR, Smith SD. Evaluation of the influence of pharmacists and GPs on patient perceptions of long-term topical corticosteroid use. *J Dermatolog Treat*. 2017;28:112-118.
28. Mueller SM, Itin P, Vogt DR, et al. Assessment of ''corticophobia'' as an indicator of non-adherence to topical corticosteroids: a pilot study. *J Dermatolog Treat*. 2017;28:104-111.
29. Stalder JF, Bernier C, Ball A, et al. Therapeutic patient education in atopic dermatitis: worldwide experiences. *Pediatr Dermatol*. 2013;30:329-334.
30. Staab D, Diepgen TL, Fartasch M, et al. Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. *BMJ*. 2006;332:933-938.
31. Ersser SJ, Cowdell F, Latter S, et al. Psychological and educational interventions for atopic eczema in children. *Cochrane Database Syst Rev*. 2014;(1):CD004054.
32. Heratizadeh A, Werfel T, Wollenberg A, et al. Effects of structured patient education in adults with atopic dermatitis: multicenter randomized controlled trial. *J Allergy Clin Immunol*. 2017; http://dx.doi.org/10.1016/j.jaci.2017.01.029 [E-pub ahead of print].
33. Langan SM, Silcocks P, Williams HC. What causes flares of eczema in children? *Br J Dermatol*. 2009;161:640-646.
34. Devillers AC, Oranje AP. Wet-wrap treatment in children with atopic dermatitis: a practical guideline. *Pediatr Dermatol*. 2012;29:24-27.
35. Paller AS, Eichenfield LF, Kirsner RS, et al. Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis: a new paradigm for use. *Pediatrics*. 2008;122:e1210-e1218.
36. Hanifin J, Gupta AK, Rajagopalan R. Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. *Br J Dermatol*. 2002;147:528-537.
37. Berth-Jones J, Damstra RJ, Golsch S, et al. Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *BMJ*. 2003;326:1367.
38. Wollenberg A, Reitamo S, Girolomoni G, et al. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. *Allergy*. 2008;63:742-750.
39. Wollenberg A, Ehmann LM. Long term treatment concepts and proactive therapy for atopic eczema. *Ann Dermatol*. 2012;24:253-260.
40. Graber CJ, Shane AL, Weintrub P, Chambers HF. Clonality of *Staphylococcus aureus* colonization over time in attendees of a camp for children with chronic dermatoses. *Pediatr Dermatol*. 2011;28:519-523.
41. Bieber T. Atopic dermatitis. *N Engl J Med*. 2008;358:1483-1494.
42. Kong HH, Oh J, Deming C, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res*. 2012;22:850-859.
43. Wollenberg A, Wetzel S, Burgdorf WH, Haas J. Viral infections in atopic dermatitis: pathogenic aspects and clinical management. *J Allergy Clin Immunol*. 2003;112:667-674.
44. Hauk PJ, Hamid QA, Chrousos GP, Leung DY. Induction of corticosteroid insensitivity in human PBMCs by microbial superantigens. *J Allergy Clin Immunol*. 2000;105:782-787.
45. Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, Williams HC. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema: an updated Cochrane review. *Br J Dermatol*. 2010;163:12-26.
46. Huang JT, Rademaker A, Paller AS. Dilute bleach baths for *Staphylococcus aureus* colonization in atopic dermatitis to decrease disease severity. *Arch Dermatol*. 2011;147:246-247.
47. Glatz M, Bosshard P, Schmid-Grendelmeier P. The role of fungi in atopic dermatitis. *Immunol Allergy Clin North Am*. 2017;37:63-74.
48. Correa da Rosa J, Malajian D, Shemer A, et al. Patients with atopic dermatitis have attenuated and distinct contact hypersensitivity responses to common allergens in skin. *J Allergy Clin Immunol*. 2015;135:712-720.
49. Dinkloh A, Worm M, Geier J, Schnuch A, Wollenberg A. Contact sensitization in patients with suspected cosmetic intolerance: results of the IVDK 2006-2011. *J Eur Acad Dermatol Venereol*. 2015;29:1071-1081.
50. Malajian D, Belsito DV. Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis. *J Am Acad Dermatol*. 2013;69:232-237.
51. Shaughnessy CN, Malajian D, Belsito DV. Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis: reactivity to surfactants. *J Am Acad Dermatol*. 2014;70:704-708.
52. Tintle S, Shemer A, Suarez-Farinas M, et al. Reversal of atopic dermatitis with narrow-band UVB phototherapy and biomarkers for therapeutic response. *J Allergy Clin Immunol*. 2011;128:583-593. e1-4.
53. Garritsen FM, Brouwer MW, Limpens J, Spuls PI. Photo (chemo)therapy in the management of atopic dermatitis: an updated systematic review with implications for practice and research. *Br J Dermatol*. 2014;170:501-513.
54. Meduri NB, Vandergriff T, Rasmussen H, Jacobe H. Phototherapy in the management of atopic dermatitis: a systematic review. *Photodermatol Photoimmunol Photomed*. 2007;23:106-112.
55. Ling TC, Clayton TH, Crawley J, et al. British Association of Dermatologists and British Photodermatology Group

guidelines for the safe and effective use of psoralen-ultraviolet A therapy 2015. *Br J Dermatol*. 2016; 174:24-55.

56. Darné S, Leech SN, Taylor AE. Narrowband ultraviolet B phototherapy in children with moderate-to-severe eczema: a comparative cohort study. *Br J Dermatol*. 2014;170:150-156.
57. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol*. 2012;26:1176-1193.
58. Koek MB, Buskens E, van Weelden H, Steegmans PH, Bruijnzeel-Koomen CA, Sigurdsson V. Home versus outpatient ultraviolet B phototherapy for mild to severe psoriasis: pragmatic multicentre randomised controlled non-inferiority trial (PLUTO study). *BMJ*. 2009;338:b1542.
59. Soliman A, Nofal E, Nofal A, El Desouky F, Asal M. Combination therapy of methotrexate plus NBUVB phototherapy is more effective than methotrexate monotherapy in the treatment of chronic plaque psoriasis. *J Dermatolog Treat*. 2015;26:528-534.
60. Gore C, Johnson RJ, Caress AL, Woodcock A, Custovic A. The information needs and preferred roles in treatment decision-making of parents caring for infants with atopic dermatitis: a qualitative study. *Allergy*. 2005;60:938-943.
61. Garritsen TK, van den Broek MPH, van Zuilen AD, Fidder HH, de Bruin-Weller MS, Spuls PI. Pregnancy and fetal outcomes after paternal exposure to azathioprine, methotrexate or mycophenolic acid: a critically appraised topic. *Br J Dermatol*. 2017;176:866-877.
62. Simpson EL, Gadkari A, Worm M, et al. Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): a phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). *J Am Acad Dermatol*. 2016;75:506-515.
63. Gerbens LA, Boyce AE, Wall D, et al. TREatment of ATopic eczema (TREAT) Registry Taskforce: protocol for an international Delphi exercise to identify a core set of domains and domain items for national atopic eczema registries. *Trials*. 2017;18:87.